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Authors
Parchem, Jacqueline G
Sparks, Teresa N
Gosnell, Kristen
et al.

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Utility of chromosomal microarray in anomalous fetuses

Jacqueline G. Parchem[1,2,*], **Teresa N. Sparks**[1,3], **Kristen Gosnell**[4], and **Mary E. Norton**[1,3]

[1]Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco, CA 94158

[2]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX 77030

[3]Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco, CA 94158

[4]Fetal Treatment Center, Benioff Children's Hospital, University of California, San Francisco, CA 94158

Abstract

Objective—To determine the association of copy number variants (CNV) with perinatal outcomes among fetuses with sonographic abnormalities.

Methods—This was a retrospective cohort study of anomalous fetuses evaluated at a single fetal center, who underwent chromosomal microarray (CMA) testing. Pathogenic CNV or variants of uncertain significance (VUS) were classified as abnormal. The primary outcome of perinatal death was compared among fetuses with normal versus abnormal CMA. Secondary outcomes included preterm birth, small for gestational age birth weight, and death prior to discharge. The odds ratio (OR) of perinatal death was determined, adjusting for potential confounders.

Results—Of 280 fetuses, 60 (21.4%) had abnormal CMA results – 21 (35.0%) were classified as pathogenic, 39 (65.0%) were VUS. Among 212 (75.7%) continuing pregnancies, abnormal CMA was not associated with increased odds of perinatal death (adjusted OR 0.81, 95% CI 0.34-1.93), after adjustment for the presence of hydrops and specific anomalies. The overall frequency of perinatal death was 21.2%. No differences in secondary outcomes were observed.

Conclusions—Abnormal CMA was not associated with increased odds of perinatal death in this cohort. Fetal CNV are common among fetal center patients; such fetuses are at high risk of perinatal death irrespective of CMA results.

Corresponding Author: Jacqueline Parchem, MD, 6431 Fannin St, MSB 3.286, Houston, TX 77030, Phone: (415) 250-6257, jparchem@mdanderson.org, jackieparchem@gmail.com.

*Current affiliations: Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences, McGovern Medical School at The University of Texas Health Science Center at Houston, TX 77030; Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

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Introduction

Chromosomal microarray (CMA) has become the first-tier genetic test for the evaluation of fetuses and children with congenital anomalies and neurodevelopmental disorders[1,2]. CMA provides genetic information at a higher resolution than conventional karyotyping by detecting copy number variants (CNV) – submicroscopic chromosomal deletions or duplications – as small as 50-100 kilobases. CNV are interpreted as benign, pathogenic, or variants of uncertain significance (VUS) depending on the specific location, genes affected, and the level of existing evidence linking the variant with a phenotype. The introduction of CMA into clinical practice over the past decade has significantly increased the diagnostic yield of genetic testing in several scenarios, including cases of congenital anomalies, stillbirth, cerebral palsy, intellectual disability, developmental delay, and autism spectrum disorders[3–8]. CMA may also be of diagnostic utility in the setting of nonimmune hydrops fetalis (NIHF)[5,9].

CMA has been shown to detect clinically relevant deletions or duplications in 6% of euploid fetuses with one or more structural anomalies, and is routinely recommended when anomalies are detected by prenatal ultrasound[1,2,6]. While an abnormal fetal karyotype in this setting is often associated with an increased risk of perinatal demise, it is uncertain if CNV have the same implications[10,11]. Understanding the prognostic impact of these genetic abnormalities may provide clarity for expectant families, shape expectations, and serve as a basis for counseling regarding the risk of recurrence in future pregnancies. The likelihood of survival is particularly important, and may guide critical clinical management decisions, such as choosing comfort care, in utero therapy, or aggressive resuscitation at birth. Whether CMA is a useful predictor of outcomes, including survival, in fetuses with anomalies is unknown.

The objective of this study was to evaluate the association of CMA with perinatal death among anomalous fetuses, as well as with additional outcomes, including mode of delivery, preterm birth, small for gestational age (SGA) birth weight, prolonged hospitalization, and death prior to discharge from the hospital. We hypothesized that fetuses with abnormal CMA results would have a greater risk of perinatal death and other adverse perinatal outcomes.

Methods

This was a retrospective cohort study of fetuses with structural anomalies or NIHF identified on prenatal ultrasound, who underwent genetic evaluation with CMA. Patients referred to the University of California, San Francisco (UCSF) Fetal Treatment Center (FTC) with estimated due dates between January 1, 2011 and September 1, 2016 were identified through the FTC database and evaluated for inclusion. Inclusion criteria were singleton or twin pregnancies with at least one fetal structural anomaly or NIHF for which a prenatal or postnatal CMA was performed. Monochorionic-diamniotic and dichorionic-diamniotic twin pregnancies were included, with outcomes analyzed per pregnancy (all of these cases involved only one anomalous fetus). Pregnancies for which fetal anomalies were not confirmed by ultrasound at our institution, information regarding pregnancy outcome or

perinatal survival were unobtainable, and cases in which hydrops was attributable to isoimmunization or twin-twin transfusion syndrome (TTTS) were excluded.

The primary outcome of interest was perinatal death, defined as stillbirth or neonatal death within the first 28 days of life. Secondary outcomes were mode of delivery, preterm birth <37 weeks, SGA birth weight, prolonged hospitalization, and death prior to discharge from the hospital among those who survived beyond the neonatal period. SGA was defined as birth weight ≤10th percentile by gestational age according to Fenton growth charts[12]. Prolonged hospitalization was defined as length of stay >28 days if delivered at ≥36 weeks gestation, or greater than the number of days needed to correct the birth gestational age to 40 weeks if delivered before 36 weeks gestation among those who survived the neonatal period. Elective terminations of pregnancy were reported, but not included in analyses of the primary and secondary outcomes. Approval from the UCSF Committee on Human Research was obtained and enabled completion of this study (IRB #10-04093).

The FTC database includes comprehensive information about all patients referred to the center, including demographics, obstetric details, fetal anomalies, genetic testing, delivery outcomes, and postnatal survival. Pregnancy and neonatal outcomes were abstracted from the medical record for patients who delivered at UCSF. For those who delivered elsewhere, outcome data were obtained through the referring provider, electronic medical record, or communication with the patient. The sample size was fixed and limited to the total number of eligible pregnancies within the study period. Fetal anomalies were classified by anatomic location or affected organ system: brain, spine, face, neck, thorax, cardiac, gastrointestinal/ventral wall, genitourinary, musculoskeletal, and NIHF. Fetuses were considered to have multiple anomalies if more than one system was affected. For fetuses with NIHF, whether or not hydrops was associated with a structural anomaly was noted. Cases of hydrops associated with a structural anomaly were included in the organ system category of that anomaly.

CMA was performed on samples obtained from prenatal diagnostic procedures, or from neonatal blood collection for those cases in which prenatal testing was offered but not performed. Postnatal CMA results were included because CMA is recommended for all patients with anomalies detected on prenatal ultrasound, and we were interested in the relationship between CMA results and perinatal outcomes regardless of when that result was obtained. Due to the referral nature of our patient population, array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) microarrays were performed at a variety of laboratories, including Integrated Genetics, Quest Diagnostics, ARUP Laboratories, Signature Genomics, and Kaiser Permanente Regional Genetics Laboratory. Information regarding CMA protocols can be found through each of these individual laboratories. CMA results were classified as normal or abnormal for the purposes of this study. Cases without a CNV or with a benign CNV were classified as normal. Those with a pathogenic CNV or a VUS were considered abnormal in order to capture all potentially significant variants in the analyses. Further analyses compared outcomes among cases with pathogenic CNV versus VUS, as well as pathogenic CNV versus normal results (excluding all cases with VUS) to determine how defining VUS as abnormal may have impacted results. Individual CMA reports and CNV classifications were reviewed by a

clinical geneticist (T.N.S.). Due to evolving genetics data, additional review of currently published data through PubMed, ClinVar, and DECIPHER was performed to confirm the interpretation of results obtained prior to 2014. This review did not lead to reclassification of results, perhaps partly due to incomplete information about genomic coordinates in some cases.

Baseline characteristics and perinatal outcomes were compared for normal and abnormal CMA groups using Fisher's exact test or χ^2 test for categorical variables, and Student's *t*-test for continuous variables. Multivariable logistic regression was used to estimate the odds of perinatal death in the setting of abnormal CMA results, with adjustment for confounders. Selection of potential confounders was based upon results from univariable analyses, as well as risk factors for the primary outcome that have been reported in the literature. Confounders included in the models were the presence of hydrops and specific types of anomalies (cardiac defects, congenital diaphragmatic hernia (CDH), brain anomalies, facial anomalies, and genitourinary anomalies). Adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were reported. All tests were two-tailed and a *P* value of <0.05 was considered significant. STATA 13.1 was used to perform analyses.

Results

There were 304 fetuses identified with CMA results, of which 24 were excluded for the following reasons: a change in the referral diagnosis (i.e. normal ultrasound) upon evaluation at our center (n=8), referral without evaluation (n=6), TTTS without anomalies in either fetus (n=2), monoamniotic twin or triplet gestation (n=4), or perinatal outcome unknown (n=4). Primary outcome data were available for 280 pregnancies (Figure 1). Sixty (21.4%) had abnormal CMA results, including 21 (7.5%) pathogenic and 39 (13.9%) VUS.

Baseline clinical characteristics of the study cohort are shown in Table 1. Normal and abnormal CMA groups were similar with respect to maternal age, parity, fetal sex, presence of multiple anomalies, and types of anomalies. The majority of results were based on prenatal diagnostic testing (72.5%). All patients with postnatal CMA had testing done prior to hospital discharge. A higher proportion of patients with abnormal CMA had postnatal testing compared to those with normal CMA, 55% vs. 20% (*P*<0.001), respectively. Most fetuses that were tested prenatally had normal CMA results (176/203, 86.7%).

Overall, 68 (24.3%) women elected termination of pregnancy. Outcomes for the remaining 212 ongoing pregnancies are shown in Table 2. The overall frequency of perinatal death was high (21.2%), and similar between pregnancies with abnormal and normal CMA results (19.6% vs. 21.7%, *P*=0.85). There were 14 (6.6%) stillbirths and 31 (14.6%) neonatal deaths; no difference in the frequency of either of these outcomes was found between the groups. Among 55 preterm neonates, 16 (29.1%) died in the neonatal period (35.7% with abnormal CMA group vs. 26.8% in the normal group, *P*=0.52). The odds of perinatal death were not increased in the context of abnormal CMA results (unadjusted OR 0.88, 95% CI 0.40-1.93). This finding remained after adjustment for potential confounders, including hydrops and specific types of anomalies: cardiac defects, CDH, brain, facial, and genitourinary tract anomalies (aOR 0.81, 95% CI 0.34-1.93). Factors independently

associated with an increased risk of perinatal death were hydrops (aOR 9.11, 95% CI 3.03-27.44), CDH (aOR 2.98, 95% CI 1.31-6.79), and genitourinary anomaly (aOR 2.92, 95% CI 1.04-8.23).

We also did not observe differences in the secondary outcomes examined when abnormal CMA was compared with normal, including mode of delivery, preterm birth, SGA birth weight, prolonged hospitalization, and death prior to discharge from the hospital (Table 2). Overall, Cesarean delivery occurred in 50% of pregnancies, and approximately 40% of infants who survived the neonatal period required prolonged hospitalization. When we excluded VUS and examined only pathogenic CNV versus normal CMA cases, our results were similar; the presence of a pathogenic CNV was not associated with perinatal death, and the specific anomalies found to be independent predictors of perinatal mortality risk when VUS were included remained associated. To evaluate the effect of including twin pregnancies, a stratified analysis of singleton pregnancies was performed, which revealed no differences in results when twins were excluded.

Outcomes for abnormal CMA cases were further examined by CNV classification (Table 3). Among fetuses with an abnormal CMA result, a pathogenic variant was identified in 21 subjects (35.0%), and a VUS was found in 39 (65.0%). There were no significant differences in primary or secondary outcomes between subjects with pathogenic variants vs. VUS. Table 4 details the specific CNVs and types of anomalies for cases of perinatal death and death prior to hospital discharge, including the most detailed CNV information available. In some cases where women were referred from outside institutions, the full CMA report including genomic coordinates was not available. Additional CNV information for the remaining abnormal cases is provided in Appendix A.

Cardiac defects, and anomalies of the thorax (mostly CDH) and brain were the most common abnormalities, affecting 36.4%, 29.3%, and 20.0% of the cohort, respectively (Figure 2). Multiple anomalies were present in 90 (32.1%) pregnancies, 25 (27.8%) of which had an abnormal CMA. Of 21 cases with NIHF, 3 (14.3%) had abnormal CMA results. An underlying structural anomaly was thought to be the etiology of NIHF in 11 cases (52%), whereas hydrops was an isolated finding in 10 cases. Ten of 45 (22.2%) perinatal deaths in the cohort occurred in subjects with NIHF, including 5 stillbirths and 5 neonatal deaths.

A prenatal therapeutic procedure was performed in 30 of the pregnancies (10.7%), including thoracentesis ± shunt (n=8), open neural tube defect repair (n=4), vesicocentesis ± shunt (n=4), percutaneous umbilical blood sampling ± intrauterine transfusion (n=4), fetoscopic balloon tracheal occlusion for CDH (FETO; n=3), aortic valvuloplasty (n=3), laser ablation for TTTS (n=2), and radiofrequency ablation for severe, selective growth restriction of an anomalous donor twin (n=2; Table 5). All but 2 of these subjects had a normal CMA (93.3%, P=0.04). The enrichment of normal CMA in this subgroup may be due to the recommendation for normal genetic evaluation prior to some of the interventions, including myelomeningocele repair, FETO for CDH, and vesicoamniotic shunt placement for lower urinary tract obstruction. Among the 26 pregnancies that were continued following intervention, there were 5 perinatal deaths (19.2%), all with normal CMA. This rate did not

differ significantly from the perinatal death rate among pregnancies that did not undergo intervention (40 deaths out of 186 ongoing pregnancies, 21.5%; $P>0.99$).

Discussion

We investigated the prognostic value of CMA in fetuses with sonographic abnormalities in a diverse cohort of pregnancies across a >5-year time span. A pathogenic variant or VUS was detected in over 20 percent of cases, with the majority being a VUS. Among fetuses with and without abnormal CMA results, we found no difference in perinatal death, or the secondary outcomes of mode of delivery, preterm birth, SGA birth weight, prolonged hospitalization, and death prior to discharge from the hospital. Factors associated with perinatal death included hydrops and specific anomalies, such as CDH and genitourinary anomaly.

The reported prevalence of abnormal CNV in euploid fetuses with anomalies is 6-10%, although the association of CNV with specific categories of anomalies or multiple anomalies is higher[5,6,13,14]. In a recent study of infants with congenital heart disease, for example, clinically significant CNV or VUS were detected in 29% of subjects who underwent postnatal CMA testing[15]. We anticipated a high proportion of abnormal CMA results based on our high-risk study population, which was enriched for major and complex anomalies. Therefore, the 2-3-fold higher frequency of CMA abnormalities and relatively poor perinatal outcomes likely reflect the nature of the cohort and the types of anomalies referred to centers specializing in fetal diagnosis and therapy, as well as the selection of more severe cases for testing.

Most of the abnormal CNV detected in our cohort were VUS, which may become reclassified over time. For instance, Wapner et al. reported that 38 of 94 cases (40.4%) of VUS were reclassified by the time their 5-year study was complete; 30 were reclassified as clearly pathogenic, and 8 as likely benign[6]. We reviewed older CMA results (obtained prior to 2014) in our cohort, however, none of the 23 cases had sufficient new data to be reclassified. The frequent identification of VUS is a common challenge in genetics[16], especially when identified prenatally, and patients should be informed of the potential for this finding and the limitations of their interpretation when prenatal diagnosis is undertaken.

Strengths of our study include measurement and follow up of clinically meaningful outcomes, and evaluation of a high-risk cohort. One of the challenges of studying a referral population is obtaining outcomes for patients who deliver at various hospitals. Very few of the eligible cases identified through our institutional database were lost to follow up, despite only 70% delivering at our institution.

During the study period, 1825 patients were referred to the FTC for suspected fetal anomalies. Among 1477 continuing pregnancies, there were 199 (13.5%) perinatal deaths overall; this outcome occurred in 21.2% of patients with CMA testing vs. 12.2% without testing ($P<0.001$). Among cases of perinatal death, the rate of any CMA testing was 22.6% (17.6% for prenatal CMA). The higher proportion of perinatal deaths in the CMA study cohort might be explained in part by differences in who was tested, i.e. an inclination toward

CMA testing in cases where a genetic diagnosis was strongly suspected, and not testing in the context of other anomalies where a genetic etiology was less likely and the outcomes were generally more favorable. For example, diagnostic testing is not routinely recommended for some common diagnoses, such as gastroschisis and congenital pulmonary airway malformation (CPAM). Variations in testing rates and practices may also have influenced the study cohort, as CMA was just being adopted as the first-tier genetic test for anomalous fetuses during the first half of the study[17]. Accordingly, the number of CMAs obtained increased over time. Overall, CMA (prenatal or postnatal) was performed for 280 of the 1825 (15.3%) patients referred to the FTC for suspected fetal anomalies.

The inclusion of cases for which CMA was deferred until after delivery presents the potential for selection bias. However, prenatal CMA would have been recommended for most cases in the cohort, and postnatal testing was likely performed either because the woman's preference was to defer testing until after birth, or referral to our center was made after amniocentesis had already been performed without a request for CMA. We recognize, though, that additional clinical findings after birth may have ultimately contributed to women's decisions to have a CMA performed for their neonate in some cases. Postnatal cases receiving a CMA may have been more likely to have a severe phenotype. Additionally, it is worthwhile to acknowledge that while there are not differences in the actual techniques used for postnatal versus prenatal CMA, the interpretation is somewhat different in order to decrease the rate of VUS detected in prenatal cases, while optimizing detection of clinically significant variants in postnatal cases. This difference leads to a slightly higher rate of detection of variants in postnatal cases.

Due to sample size, we were unable to determine the impact of abnormal CMA in specific subgroups of anomalies, and were underpowered to detect potential differences in some outcomes. Due to the high frequency of VUS in the abnormal group, a difference in outcomes may have been masked by grouping VUS – if ultimately benign – with pathogenic variants, as this would bias toward the null hypothesis. While this type of misclassification would underestimate the effect of abnormal CMA results, we included VUS in the abnormal group to examine the effect of all potentially clinically significant CNV. We also did not have detailed clinical information regarding pregnancy complications that may have affected outcomes, such as medical indications for preterm delivery or labor complications. The number of early preterm births (before 32 weeks), however, was limited to 8 cases (4% of livebirths) with only 1 neonatal death of a baby with a normal CMA. Therefore, we do not suspect that extremely preterm or very preterm birth had a significant impact on our results. Lastly, the limitations of retrospective chart review apply to our study, such as the potential for missing data due to differential loss to follow up, which is particularly relevant to referral populations. However, because the FTC database is actively managed with data added regularly on a prospective basis, we expect that these limitations have been minimized.

Ten percent of the cohort had a prenatal therapeutic procedure, primarily in the context of normal CMA results. Generally, these procedures are undertaken in fetuses at highest risk for a poor outcome, therefore the predominance of procedures in the normal CMA group may have skewed our findings, although the extent to which the intervention itself influenced outcomes is uncertain. An important unanswered question is what the role of

CMA prior to prenatal therapy should be. Most centers require a normal karyotype prior to in utero fetal interventions, but whether patients with abnormal CMA results should be excluded from antenatal fetal therapy has not been determined. Further investigation in this area may help to establish standards for testing and eligibility for in utero intervention.

Finally, a relatively high proportion of women elected termination of pregnancy. These were excluded from the outcomes analysis as we were unable to study the primary outcome for these pregnancies. Among women with prenatal testing results who chose termination, over 80% had a normal CMA, suggesting that most of the decisions were driven by the severity of ultrasound findings rather than CMA results. Indeed, 25% of women electing termination had CMA testing post-procedure.

In conclusion, CNV were detected in over 20% of our cohort of fetuses with major structural anomalies or NIHF, and there was a high rate of perinatal death among those with both normal and abnormal CMA results. However, we did not find an association between abnormal CMA and perinatal death, mode of delivery, preterm birth, SGA birth weight, prolonged hospitalization, or death prior to hospital discharge. Our findings suggest that although fetuses with ultrasound abnormalities are at increased risk of having a CNV detected on CMA, those with abnormal CMA results are not at greater risk of perinatal death overall compared to those with normal results. This may change over time as we gather more genetics data that will improve our ability to classify variants as benign or pathogenic, and future studies should reassess these relationships in separate populations. This study further highlights the need for comprehensive genetic counseling in each of these cases, particularly when a VUS is detected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's already known about this topic?

- Chromosomal microarray (CMA) testing increases the diagnostic yield when fetal anomalies are found on prenatal ultrasound. Information about the impact of copy number variants (CNV) on perinatal outcomes is limited.

What does this study add?

- In our study, CNV were not associated with increased odds of perinatal death among fetuses with structural anomalies or nonimmune hydrops.

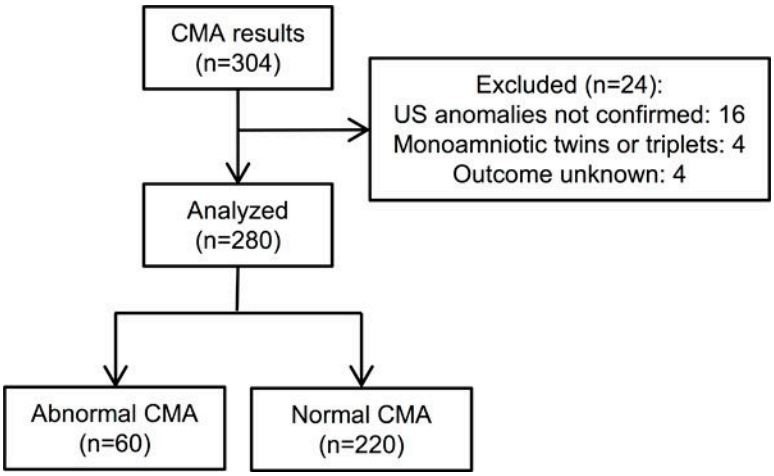

Figure 1.
Study Cohort. CMA, chromosomal microarray, US, ultrasound.

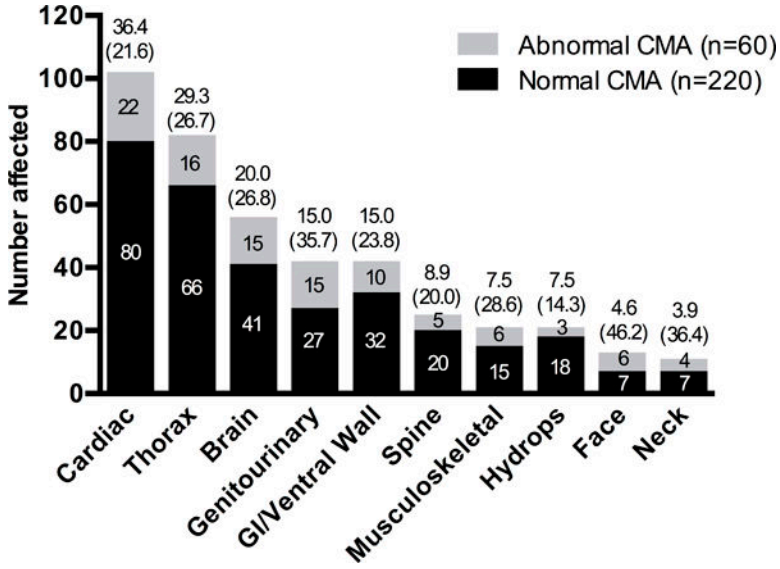

Figure 2.

Distribution of Anomalies and Chromosomal Microarray Results. CMA, chromosomal microarray. Data are n or %. Bar labels indicate the number of abnormal and normal CMA cases according to type of anomaly. Above each bar: percentage of cases in the cohort with each type of anomaly, and the percentage of cases with abnormal CMA results within that anomaly subgroup (in parentheses). Cumulative percentage >100% due to cases with multiple anomalies, which are counted more than once.

Table 1

Cohort Characteristics

Characteristic	Overall (n=280)	CMA Category		*P*
		Abnormal (n=60)	Normal (n=220)	
Maternal				
Maternal age (years)	31.2 ± 6.0	29.9 ± 6.2	31.6 ± 5.9	0.06
Nulliparous	123 (43.9)	23 (38.3)	100 (45.5)	0.38
Fetal				
Male fetus	164 (58.6)	35 (58.3)	129 (58.6)	>0.99
Twin gestation	20 (7.1)	1 (1.7)	19 (8.6)	0.09
Multiple anomalies	90 (32.1)	25 (41.7)	65 (29.6)	0.09
Single system anomaly				
Brain	26 (9.3)	2 (3.3)	24 (10.9)	0.08
Spine	9 (3.2)	0	9 (4.1)	0.21
Face	3 (1.1)	0	3 (1.4)	>0.99
Neck	2 (0.7)	0	2 (0.9)	>0.99
Thorax	49 (17.5)	8 (13.3)	41 (18.6)	0.44
Cardiac	53 (18.9)	12 (20.0)	41 (18.6)	0.85
GI/Ventral wall	14 (5.0)	6 (10.0)	8 (3.6)	0.09
Genitourinary	19 (6.8)	5 (8.3)	14 (6.4)	0.57
Musculoskeletal	5 (1.8)	1 (1.7)	4 (1.8)	>0.99
Hydrops	10 (3.6)	1 (1.7)	9 (4.1)	0.70
Prenatal microarray	203 (72.5)	27 (45.0)	176 (80.0)	<0.001
Prenatal therapeutic procedure[†]	30 (10.7)	2 (3.3)	28 (12.7)	0.04

CMA, chromosomal microarray; GI, gastrointestinal.

Data are mean ± standard deviation or n (%).

[†]Including thoracentesis ± shunt, open neural tube defect repair, vesicocentesis ± shunt, percutaneous umbilical blood sampling ± intrauterine transfusion, fetoscopic balloon tracheal occlusion, aortic valvuloplasty, laser ablation for twin-twin transfusion syndrome, and radiofrequency ablation for severe, selective growth restriction of anomalous donor twin.

Table 2

Perinatal Outcomes by CMA Result

Outcome	Overall	CMA Category		*P*	aOR[†] (95%CI)
		Abnormal	Normal		
CMA (n)	280	60	220		
Termination of pregnancy	68 (24.3)	9 (15.0)	59 (26.8)	0.06	
Ongoing pregnancies (n)	212	51	161		
Perinatal death	45 (21.2)	10 (19.6)	35 (21.7)	0.85	0.81 (0.34-1.93)
Stillbirth	14 (6.6)	3 (5.9)	11 (6.8)	>0.99	1.38 (0.35-5.50)
Neonatal death	31 (14.6)	7 (13.7)	24 (14.9)	>0.99	1.00 (0.38-2.65)
Livebirths (n)	198	48	150		
Cesarean delivery	99 (50.0)	22 (45.8)	77 (51.3)	0.63	
Preterm birth <37 weeks	55 (27.8)	14 (29.2)	41 (27.3)	0.85	
Small for gestational age	30 (15.1)	7 (14.6)	23 (15.3)	0.83	
Survived neonatal period (n)	167	41	126		
Prolonged hospitalization[‡]	66 (39.5)	22 (53.7)	44 (34.9)	0.11	
Death prior to discharge	11 (6.6)	5 (12.2)	6 (4.8)	0.22	

CMA, chromosomal microarray; aOR, adjusted odds ratio; CI, confidence interval.

Data are n (%) unless otherwise specified.

Number of missing values: Cesarean delivery, 1 (normal CMA); small for gestational age, 22 (18 normal, 4 abnormal); prolonged hospitalization, 35 (29 normal, 6 abnormal); death prior to discharge, 31 (25 normal, 6 abnormal).

[†]Adjusted for the presence of hydrops, cardiac defects, congenital diaphragmatic hernia, brain, facial, and genitourinary anomalies.

[‡]Prolonged hospitalization defined as length of stay >28 days if delivered at ≥36 weeks gestation or > the number of days needed to correct birth gestational age to 40 weeks if delivered at <36 weeks gestation among those who survived the neonatal period.

Table 3

Perinatal Outcomes for Abnormal CMA Group by Variant Type

Outcome	Overall	Pathogenic	VUS	*P*
Abnormal CMA (n)	60	21	39	
Termination of pregnancy	9 (15.0)	4 (19.1)	5 (12.8)	0.71
Ongoing pregnancy (n)	51	17	34	
Perinatal death	10 (19.6)	2 (11.8)	8 (23.5)	0.46
Stillbirth	3 (5.9)	1 (5.9)	2 (5.9)	>0.99
Neonatal death	7 (13.7)	1 (5.9)	6 (17.7)	0.40
Livebirths (n)	48	16	32	
Cesarean delivery	22 (45.8)	7 (43.8)	15 (46.9)	>0.99
Preterm birth <37 weeks	14 (29.2)	5 (31.3)	9 (28.1)	>0.99
Small for gestational age	7 (14.6)	3 (18.8)	4 (12.5)	0.87
Survived neonatal period (n)	41	15	26	
Prolonged hospitalization[†]	22 (53.7)	8 (53.3)	14 (53.9)	0.21
Death prior to discharge	5 (12.2)	2 (13.3)	3 (11.5)	0.25

CMA, chromosomal microarray; VUS, variant of uncertain significance.

Data are n (%) unless otherwise specified.

Number of missing values: small for gestational age, 4 (1 pathogenic, 3 VUS); prolonged hospitalization, 6 (4 pathogenic, 2 VUS); death prior to discharge, 6 (4 pathogenic, 2 VUS).

[†]Prolonged hospitalization defined as length of stay >28 days if delivered at ≥36 weeks gestation or > the number of days needed to correct birth gestational age to 40 weeks if delivered at <36 weeks gestation among those who survived the neonatal period.

Table 4

CNV for Cases of Death During the Perinatal Period or Prior to Hospital Discharge[†]

Outcome	CNV Region	Size (Mb), Dup/Del	Genomic Coordinates	Anomalies/Diagnosis
Stillbirth (n=3)	Pathogenic			
	4p16.3p14	34.8 del	(249,494−35,018,295)×1	Heart, 2-vessel cord; Wolf-Hirschhorn syndrome
	VUS			
	3q29 15q24.3	0.42 dup 0.56 del	(196,892,569−197,317,103)×3 (76,659,792−77,220,569)×1	Heart, hydrops; MYH7 mutation (familial)
	14q13.1q24.2	0 (UPD)	(34,635,871-70,754,507)×2 hmz	Multiple (limb body wall complex)
Neonatal Death (n=7)	Pathogenic			
	22q11.2	2.83 dup	(18,636,748-21,465,659)×3	Multiple (brain, heart, CDH, GU)
	VUS			
	1p36.11	0.25 del (mosaic)	(26,797,508-27,052,080)×1~2	Multiple (brain, spine, CDH)
	11p11.2	0.55 del	(46,862,035-47,414,071)×1	Hydrops; PTPN11 mutation heterozygote - Noonan spectrum
	15q25.2q25.3	Del		CDH
	16q22.3q23.1	0.29 dup	(73,976,130-74,270,043)×3; 14.9% regions of hmz	Multiple (brain, GU); PEX1 mutation - peroxisome biogenesis disorder
	16q23.1q23.2	2.7 del		Multiple (brain, neck, abdomen)
	Yq11.223 Yq11.223q11.23 Yq11.23	0.49 dup 0.50 dup 0.39 dup (mosaic)	(24,865,133-25,356,566)×1~2 (25,767,755-26,269,355)×1~2 (26,942,331-27,328,305)×1~2	Multiple (CDH, GU, musculoskeletal)
Death After the Neonatal Period (n=5)[‡]	Pathogenic			
	22q11.21	0.73 del	(20,728,956-21,461,659)×1	Multiple (CDH, GU)
	22q 15q (VUS)	3.02 del 0.43 dup		Heart (TOF, absent pulmonary valve); DiGeorge syndrome
	VUS			
	10p11.21	0.26 dup	(35,099,799-35,362,977)×3	Heart (TOF)
	Xq13.3	0.27 dup	(75,092,483-75,360,248)×3	Heart (hypoplastic left heart syndrome)
	Xp22.33 Xq21.31q21.32	0.63 dup 0.28 dup	(605,803-1,232,886)×3 (91,547,112-91,823,765)×3	CDH

CNV, copy number variant; Mb, megabases; dup, duplication; del, deletion; VUS, variant of uncertain significance; UPD, uniparental disomy; hmz, homozygosity; CDH, congenital diaphragmatic hernia; GU, genitourinary; TOF, Tetralogy of Fallot.

[†]Data provided in as much detail as available. Additional CNV information for all other abnormal chromosomal microarray provided in Appendix A.

[‡]Outcomes beyond the neonatal period not known for all cases. Missing discharge information for 6 abnormal chromosomal microarray cases.

Table 5

Prenatal Therapeutic Procedures and Outcomes

Procedure	N	Abnormal CMA	Outcomes	
			Survivors[†]	Non-survivors
Open surgery				
Myelomeningocele repair	4	0	4	0
Fetoscopic balloon procedures				
Tracheal occlusion (for CDH)	3	0	3	0
Aortic valvuloplasty	3	0	3	0
Fetoscopic procedures for TTTS				
Radiofrequency ablation of anomalous donor	2	0	–	2 RFA[‡]
Laser photocoagulation	2	0	1	1 IUFD
Needle-based procedures				
Thoracentesis ± shunt	8	1	6[§]	2 NND
PUBS ± intrauterine transfusion[¶]	4	0	2	2 IUFD
Urinary tract tap ± shunt	4	1	2	2 terminations[§]
Total	30/280 (10.7)	2/30 (6.7)	21/30 (70)	9/30 (30)

CMA, chromosomal microarray; CDH, congenital diaphragmatic hernia; TTTS, twin-twin transfusion syndrome; RFA, radiofrequency ablation; IUFD, intrauterine fetal demise; NND, neonatal death; PUBS, percutaneous umbilical blood sampling.

Data are n or n (%).

[†]Survival beyond the neonatal period.

[‡]RFA of growth-restricted, anomalous donor (structurally normal recipient twin) in both cases; donors reported as non-survivors here. The recipient of one pregnancy was delivered at term and survived; the other died in the setting of previable delivery after preterm premature rupture of membranes.

[§]Includes the abnormal CMA case.

[¶]Includes intrauterine transfusion for 2 cases of anemia not due to alloimmunization (Parvovirus B19 infection in 1 case, cause of the other unknown); PUBS in 1 case of bilateral renal agenesis/anhydramnios, and 1 case of hydrops with concern for goiter.